Central Asian Journal of Medical Sciences
CAJMS

Original Article
Cent Asian J Med Sci. 2020 December;6(4):249-255. https://doi.org/10.24079/CAJMS.2020.12.006

# The Efficacy and Safety of "Kyushin" in Mongolian Patients with Ischemic Heart Disease and Heart Failure

**Altaisaikhan Khasag[1], Oyuntugs Byambasukh[1], Bayarsukh Narmandakh[1], Amarjargal Badarch[2], Tungalag Shukhert[3], Tsolmon Unurjargal[4]**

[1]Department of Endocrinology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; [2]First State Hospital Mongolia, Ulaanbaatar, Mongolia; [3]Express Laboratory, Ulaanbaatar, Mongolia; [4]Department of Cardiology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia

**Submitted:** June 25, 2020
**Revised:** July 3, 2020
**Accepted:** November 30, 2020

**Corresponding Author**
Altaisaikhan Khasag, MD, PhD
Department of Endocrinology, School of Medicine, Mongolian National University of Medical Sciences, Ulaanbaatar 14210, Mongolia
**Tel:** +976-9990169
**E-mail:** altaisaikhan@mnums.edu.mn



**Objectives:** This study aimed to investigate the efficacy and safety of Kyushin in addition to conventional drug therapy. **Methods:** This study included 109 (Male/Female = 44/65) subjects were assigned to two groups (Kyushin and conventional treatment vs. conventional treatment alone) based on age, gender, and initial physiologic test values. Subjects in the Kyushin group received Kyushin 30 mg orally three times daily for eight weeks. Subjective complaints, physiological examinations (ECG, echocardiography, blood pressure, pulse rate) and laboratory tests were conducted at the start of the study and after eight weeks of treatment. The pre- and post-treatment Kyushin results were compared with the conventional treatment group's findings. **Results:** In the patients treated with Kyushin, significant improvements were observed in these subjective complaints, physiological examinations (ECG, echocardiography, blood pressure, pulse rate) and laboratory tests. No adverse effects were observed during this study. **Conclusions:** This study shows that Kyushin is not only safe, it is more effective than conventional treatment alone in patients with ischemic heart disease and heart failure.

**Keywords:** Myocardial Ischemia, Heart Failure, Traditional Medicine, Cardiovascular Medicine, Mongolia

## Introduction

Ischemic heart disease and heart failure are the leading cause of cardiovascular mortality not only in Mongolia but in Asia and worldwide [1]. Some studies have shown that the drug named "Kyushin" improves palpitations, shortness of breath and acts as a restorative in patients with ischemic heart disease and heart failure. This product has been on the market for 58 years without a prescription in several Asian countries and has been used safely. Kyushin contains various plant and animal ingredients and has been used for over 100 years in Japan [2]. The standard formulation used in Japan contains toad cake 5 mg, bezoar 3 mg, ginseng 25 mg, velvet horn 5mg, pearls 7.5 mg, animal (hog) bile 8 mg and Borneo camphor 2.7 mg.

Kyushin has been studied in basic pharmacological studies and in few human clinical trials to date. It has been shown to have cardiotonic, antihypertensive, diuretic, analgesic, anti-fatigue and anti-tumor properties as well as produce respiratory excitation, improved cerebral blood flow and autonomic regulation, in several basic pharmacological studies [2-9], and normalization of tachycardia, improvement of dyspnea, improvement of angina pectoris symptoms in patients with congestive heart failure symptoms in clinical trials [2, 10-12]. There have been few scientific reports on its impact on drug treatment in cardiac patients at medical institutions and none in Mongolia that we are aware of.

This study's objective is to compare the safety and usefulness of Kyushin to conventional drugs in patients with ischemic heart disease and heart failure with relatively mild to moderate ischemic heart disease (NYHA III or below) or heart failure patients with shortness of breath. Our outcome measures include subjective complaints, hemodynamics, electrocardiograms, echocardiograms, water balance and the incidence of angina attacks.

## Materials and Methods

### Study design and subjects

This study population was 120 patients attending the Outpatient Department of Mongolia-Japan University Teaching Hospital in Ulaanbaatar, Mongolia. Patients who satisfied the inclusion criteria were assigned one of two groups: sixty were assigned to the Kyushin treatment group and sixty in the conventional treatment group, according to their age and gender, complaints and lab values. The patients were assigned to avoid significant differences biasing the study groups. Patients were included in the study if they between the ages 40 to 80 years at the time of the study, diagnosed with ischemic heart disease at NYHA III or below and heart failure and had one or more of the following indefinite complaints: fatigue/malaise, swelling, shortness of breath, distress, insomnia, cold hands and feet, sweating, dizziness, headache, and head gravity. Patients were excluded from the study if they were taking over-the-counter supplements or vitamins that could affect the results of the study, had a history of serious diseases involving the heart, liver, kidneys, or digestive organs, were pregnant or breastfeeding, had extremely irregular dietary habits - such as long shift workers or night shift workers, or were allergic to drugs and foods [13-14].

Before treatment, the patients completed several questionnaires (medical history including medications and allergies, complications of medical treatment, and dietary habits), and underwent anthropometric measurements (body height, weight and BMI), had physiological examinations (physical examination with blood pressure and pulse, ECG, and echocardiography) and laboratory tests (hematology, biochemistry and urine analysis).

Our study's primary endpoint was the assessment of changes in subject's indefinite complaints while the secondary endpoints were changes in the objective findings (laboratory results – total cholesterol, triglycerides, HDL-C and NT-pro BNP; ECG results - prolonged QRS duration, abnormal QRS-T angle, ST/T-wave abnormalities, left-axis deviation, and left bundle-branch block; and echocardiography results – ejection fraction, stroke volume, cardiac output). Assessment of these endpoints occurred when each patient began the study and after eight weeks of treatment. Any adverse reactions were recorded.

We considered prolonged QRS duration, abnormal QRS-T angle, ST/T-wave abnormalities, left-axis deviation, and left bundle-branch block as heart failure indicators. Post-treatment results were considered successful if two or more ECG abnormalities resolved, effective if any of the abnormalities resolved, ineffective if no improvement in ECG was observed, and an exacerbation if new ECG abnormalities appeared.

### Study protocol

Dosage and administration: Patients in the Kyushin group were given Kyushin 30 mg orally in the morning, evening, and before

bedtime, with approximately 150 mL of water or warm water for eight consecutive weeks. The Kyushin was supplied by Kyushin Pharmaceutical Co., Ltd, Japan. They were instructed to stop taking their current cardiac medications, except for short-acting nitrates. Patients in the conventional group were instructed to continue taking their current cardiac medications. All patients were evaluated by assessing their endpoints at the beginning of the study and eight weeks after. Patients in both groups were instructed to visit the clinic every month.

### Statistical analysis

Statistical analyses for anthropometric measurements, objective finding improvement and physiological examinations and urinalysis comparisons before and after treatment were conducted by paired t-tests; comparisons between the study groups were conducted by unpaired t-tests. Where data were used in multiple comparisons, the critical p-value was adjusted using the Bonferroni method. The chi-square test was used to compare proportions in the categorical variables and indefinite complaints. All statistical analyses were carried out using IBM SPSS version 24.0 (IBM, Chicago, IL). The level of statistical significance was set at $p < 0.05$.

### Ethical statement

Our study was conducted in compliance with the Declaration of Helsinki and the Ethical Guidelines for Research on Human Medicine, referring to the Ministerial Ordinance on Good Clinical Practice (GCP) for Drug Clinical Trials. The study protocol was reviewed and approved by the Mongolian National University of Medical Sciences Research Ethics Committee on April 16, 2019 (N038) and was conducted to protect of human rights of the subjects. All participants provided their written, informed consent.

## Results

A total of 109 (91%) of the 120 patients with ischemic heart disease and heart failure initially enrolled in the study completed the study. Fifty-five were assigned to the Kyushin treatment group and 54 to the conventional treatment group. Table 1 shows the general characteristics of the study groups. There were 65 females and 44 males. Their mean age was 59 years. There were no statistically significant differences between the study groups' characteristics upon enrollment.

**Table 1.** General characteristics of the treatment groups at the study's beginning.

| Characteristics | Kyushin Group (n = 55) | Conventional Group (n = 54) | p-value |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Age (year) | 59.23 ± 11.6 | 59.4 ± 10.5 | NS |
| Height (cm) | 161.9 ± 9.6 | 160.5 ± 10.4 | NS |
| Body weight (kg) | 79.04 ± 15.7 | 80.3 ± 20.9 | NS |
| BMI (kg/m2) | 30.14 ± 5.5 | 30.8 ± 6.9 | NS |
| Waist circumference (cm) | 102.1 ± 11.4 | 100.3 ± 15.1 | NS |
| Systolic BP (mm Hg) | 149.8 ± 16.6 | 147.23 ± 19.8 | NS |
| Diastolic BP (mm Hg) | 94.35 ± 12.4 | 92.9 ± 15.9 | NS |
| Heart rate | 101.5 ± 9.5 | 102.4 ± 10.3 | NS |
| SpO2 (%) | 94.3 ± 1.6 | 94.05 ± 2.1 | NS |
| | N (%) | N (%) | |
| Gender: male | 22 (40) | 22 (41) | NS |
| Alcohol use | 10 (18) | 12 (22) | NS |
| Smokers | 15 (27) | 18 (33) | NS |

Note: Data are presented as mean ± SD. NS: Non-significant using t-tests for continuous variables and chi-square tests for categorical.

All of the symptoms and signs of ischemic heart disease and heart failure were significantly improved in the Kyushin treatment group compared to the conventional treatment group (Table 2). The most striking reduction was for patients who no longer complained of dizziness (63%), fatigue (57%) and headache (49%). Statistically significant improvements were observed in the objective measurements, including a decrease in body weight (-7%), systolic blood pressure (-15%), diastolic blood pressure (-13%) and heart rate (-22%).

**Table 2.** Symptoms and signs of subjects before and after eight weeks of Kyushin treatment.

| | Number of cases (n = 55) | | |
|---|---|---|---|
| Symptoms and signs | Pre-treatment | Post-treatment | Difference |
| | N (%) | N (%) | % |
| Fatigue | 44 (80) | 12 (22) | - 58* |
| Edema | 46 (84) | 35 (64) | - 20 |
| Shortness of breath | 44 (88) | 35 (64) | - 24 |
| Dizziness | 53 (96) | 12 (22) | - 74* |
| Insomnia | 49 (89) | 30 (55) | - 34 |
| Sweating | 41 (75) | 35 (64) | - 11 |
| Palpations | 47 (85) | 25 (45) | - 40 |
| Headache | 41 (75) | 14 (25) | - 50* |
| | Mean ± SD | Mean ± SD | |
| Body weight | 81.3 ± 11.4 | 75.8 ± 12.1 | - 7† |
| Systolic BP | 150.1 ± 14.9 | 127.8 ± 12.1 | - 15† |
| Diastolic BP | 94.2 ± 13.9 | 81.9 ± 11.2 | - 13† |
| Heart rate | 101 ± 9.8 | 79 ± 8.4 | - 22† |

Note: Difference = 100 * (post-treatment N – pre – treatment N) / pre-treatment N; †p < 0.001 using paired t-test; †p < 0.001 using chi-square test

Regarding improvements in the ECG, Kyushin treatment resulted in a successful result in 5 (9.3%) of the Kyushin treated group compared to 3 (5.8%) of the conventionally treated group ($p < 0.05$) and Kyushin treatment resulted in an effective outcome in 25 (46.3%) of the Kyushin treated group compared to 17 (34.6%) of the conventionally treated group ($p < 0.05$). Kyushin also resulted in fewer ineffective outcomes than conventional treatment (45.0% vs. 56.0, $p < 0.05$), while 2 (3.8%) of the conventionally treated group experienced a worsening of their ECG findings compared to none of the Kyushin-treated group (Figure 1).

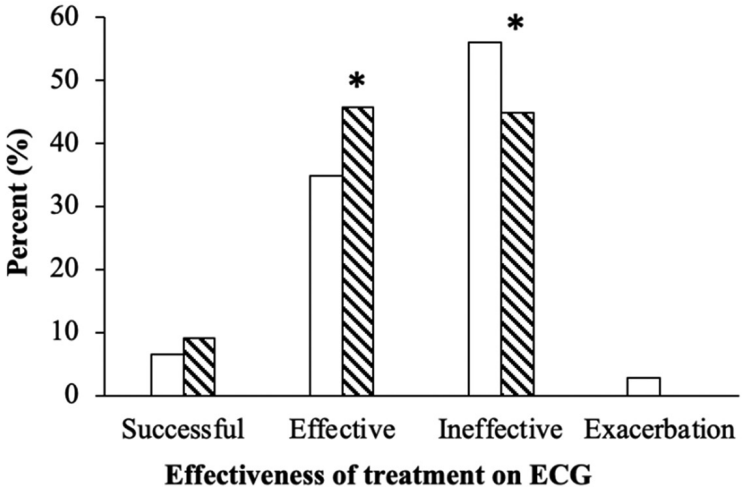


**Figure 1.** ECG improvement after 8-weeks of Kyushin or conventional treatment conventional and Kyushin treatment groups. Note: open bar indicates conventional groups, and the dashed bar indicates Kyushin treatment groups. *indicates $p < 0.05$ using the chi-square test. We considered prolonged QRS duration, abnormal QRS-T angle, ST/T-wave abnormalities, left-axis deviation, and left bundle-branch block as heart failure indicators. Post-treatment results were considered successful if two or more ECG abnormalities resolved, effective if the abnormalities resolved, ineffective if no improvement in ECG was observed, and exacerbated if new ECG abnormalities appeared.

The ECHO results showed highly statistically significant improvements in all the cardiac function parameters, most notably a 7.0 ± 5.2% increase in ejection fraction in patients receiving Kyushin compared to 2.5 ± 4.2% for the conventionally-treated patients ($p < 0.001$) (Table 3).

**Table 3.** ECHO cardiac function parameters after eight weeks of Kyushin or conventional treatment.

| | | | Treatment | | | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Treatment Group** | **N** | **Pre-** | **Post-** | **Difference** | ***p-value** | **†p-value** |
| EF (%) | Kyushin | 55 | 55.1 ± 11.7 | 62.1 ± 11.5 | 7.0 ± 5.2 | 0.001 | 0.001 |
| | Conventional | 54 | 54.3 ± 12.3 | 57.8 ± 13.4 | 2.5 ± 4.2 | 0.001 | |
| SV: mL | Kyushin | 55 | 58.5 ± 12.9 | 65.3 ± 13.9 | 7.11 ± 14.9 | 0.001 | 0.001 |
| | Conventional | 54 | 59.1 ± 11.8 | 64.2 ± 11.5 | 5.21 ± 12.3 | 0.001 | |
| CO: L/min | Kyushin | 55 | 4.11 ± 1.24 | 4.82 ± 1.34 | 0.73 ± 1.15 | 0.001 | 0.001 |
| | Conventional | 54 | 4.24 ± 1.16 | 4.38 ± 1.41 | 0.12 ± 1.12 | 0.002 | |

Note: Difference = post-treatment – pre-treatment; EF: ejection of fraction rate; SV: stroke volume; CO: cardiac output; *paired t-tests comparing pre- and post-treatment groups within rows; †independent t-tests comparing the difference in Kyushin and conventional groups after treatment; all p-values shown are significant after Bonferroni adjustment for multiple comparisons.

Likewise, there were significant improvements in the total cholesterol, HDL, and NT-proBNP observed in the Kyushin treatment group compared to the conventional treatment group, with total cholesterol improving the most with the total cholesterol in Kyushin treated patients decreasing by 0.22 ± 1.47 mmol/L compared to -0.02 ± 1.61 mmol/L for conventionally-treated patients (p=0.002) (Table 4).

**Table 4.** Laboratory test parameters before and after eight weeks of Kyushin or conventional treatment.

| | | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Pre- | Post- | Difference | | |
| **Parameter** | **Group** | **N** | **Mean ± SD** | **Mean ± SD** | **Mean ± SD** | ***p-value** | **†p-value** |
| TC: mmol/L | Kyushin | 55 | 4.86 ± 1.58 | 4.64 ± 1.41 | -0.22 ± 1.47 | 0.002 | 0.002 |
| | Conventional | 54 | 4.85 ± 1.60 | 4.82 ± 1.32 | -0.02 ± 1.61 | 0.051 | |
| TG: mmol/L | Kyushin | 55 | 1.78 ± 1.15 | 1.81 ± 1.54 | 0.03 ± 1.10 | 0.002 | 0.028 |
| | Conventional | 54 | 1.80 ± 1.21 | 1.89 ± 1.64 | 0.09 ± 1.21 | 0.001 | |
| HDL-C: mmol/L | Kyushin | 55 | 1.26 ± 0.43 | 1.28 ± 0.41 | 0.02 ± 0.038 | 0.042 | 0.032 |
| | Conventional | 54 | 1.27 ± 0.38 | 1.28 ± 0.43 | 0.01 ± 0.038 | 0.039 | |
| NT-proBNP: pg/dL | Kyushin | 55 | 51.1 ± 54.2 | 38.6 ± 30.7 | 13.4 ± 34.3 | 0.000 | 0.003 |
| | Conventional | 54 | 50.9 ± 48.9 | 45.4 ± 31.5 | -5.4 ± 31.5 | 0.003 | |

Note: TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein cholesterol; NT-proBNP: N-terminal pro-B-type natriuretic peptide. *paired t-tests comparing pre- and post-treatment groups within rows. †independent t-tests comparing the difference between groups A and B after treatment; p-values shown in bold font are significant after Bonferroni adjustment for multiple comparisons.

The erythrocyte count, hematocrit value, and hemoglobin after Kyushin were not significantly different in the study groups. There was a change in Urine protein quantity before and after Kyushin administration. However, only one patient in the Kyushin group was outside the urine reference range, and the change in other parameters did not indicate abnormal renal function and was felt by the investigator to be clinically insignificant.

## Discussion

Replacing our patients' standard medications with Kyushin resulted in significant improvements in the feeling of swelling, sweating, fatigue/malaise, dizziness on standing up, cold hands/feet, dizziness, insomnia, and headache/feeling heavy. In addition to the subjective efficacy, Kyushin may also have ameliorative effects on circulatory insufficiency, body water regulation, and autonomic dysregulation. Furthermore, our results suggest that Kyushin, when compared to standard therapy, may have substantial beneficial effects for outpatient treatment of ischemic heart disease and heart failure patients in Mongolia. Although Kyushin has been shown to improve cardiac palpitations and shortness of breath (dyspnea) in previous studies [10-11,13,15], their subjects were hospitalized patients with congestive heart failure symptoms, while our participants were not hospitalized.

There were significant beneficial effects of Kyushin treatment on physiological parameters such as blood pressure and heart rate. In accordance with our results, other researchers have found significant improvements in hemodynamics in both human and animal studies [2, 5, 9, 12-13]. In animal experiments, Toad-cake-containing herbal improves blood circulation by increasing the cardiac muscle contractile force [5, 9]. Recent studies have shown the beneficial effects of Kyushin on cardiac function for other medications containing Kyushin, suggesting that Kyushin could be an alternative treatment in patients with ischemic heart disease and heart failure [16-19].

In this study, we did not find considerable safety problems in Kyushin treatment group. Furthermore, the safety of Kyushin and its ingredients have been studied and found to be safe in clinical practice [19-20]. Kyushin's effectiveness in treating indefinite complaints related to cardiovascular factors such as tissue blood circulation, water regulation, and autonomic nerve adjustment suggests that Kyushin does not pose a safety risk.

This study had several limitations. Data on lifestyle factors at the baseline and during the study was not available. Our protocol was not blinded, so the patients and the treating physicians knew what treatment the patient was taking throughout. There was no placebo control group. Future studies need to focus on double-blinding the research and providing a placebo control group. These studies need to focus on lifestyle factors such as improvements in cardiorespiratory function in patients with ischemic heart disease and heart failure during Kyushin treatment.

### Conclusion

This study suggests that Kyushin when compared with standard treatment, is not only safe, but it is also more effective in patients

with ischemic heart disease and heart failure complaints than the conventional treatment.

## Conflict of interest

The authors state no conflict of interest.

## Acknowledgments

The authors are very grateful to everyone who contributed to the completion of this study.

## References

1. Center for health Development Ulaanbaatar. Health Indicator [accessed on 20 May, 2020]. Available at: https://www.chd.mohs.mn/2019/sariin%20medee/2018eng.pdf.
2. Shimizu Y, Hayakawa T, Sudo K. Pharmacological study of a new prescription of "Kyushin" on several indefinite complaints related cardiovascular medicine - A randomized double-blind parallel-group study between the former prescriptions. Jpn Pharmacol Ther 2015; 43: 1561-74.
3. Sakanashi M. Pharmacological Effects of Kyushin, a Toad cake containing drug. (Author's translate) Kiso to Rinshol 1992; 26: 4979-5008.
4. Morishita S, Shoji M, Oguni Y, Higuchi M, Sakanashi M. Pharmacological actions of "Kyushin" a drug containing Toad Venom: Cardiotonic and arrhythmogenic effects, and excitatory effect on respiration. Am J Chinese Med 1992; 20: 245-56.
5. Sakanashi M, Noguchi K, Chibana T, Ojiri Y, Shoji M. Effects of intraduodenal administration of "Kyushin", a Senso (Toad Venom) containing drug, on systemic hemodynamics, cardiac function and myocardial oxygen consumption in anesthetized dog. Am J Chinese Med 1993; 21: 7-16.
6. Shoji M, Oguni Y, Sato H, Morishita S, Higuchi M, Sakanashi M. Pharmacological actions of "Kyushin" a drug containing Toad Venom (2): effects on urinary volume and electrolyte excretion. Am J Chinese Med 1993; 21: 17-31.
7. Morishita S, Sugimoto C, Shoji M, Hirai Y, Oguni Y, Ito C, et al. Pharmacological actions of "Kyushin" a drug containing Toad Venom (3): Effects on experimentally induced arrhythmia. Am J Chinese Med 1993; 21: 139-49.
8. Shoji M, Hosoda R, Morishita S. Prolongation of swimming time by "Kyushin", a drug containing Senso (Ch'an Su), and the related natural medicines. J Nat Med 2000; 54: 247-52.
9. Shimizu Y, Inoue E, Nonaka K, Noguchi T, Motegi J, Sudo K. Pharmacological studies of Kyushin, a crude drug containing Chan Su on experimental hypertensive rats. Jpn Pharmacol Ther 2010; 38: 523-35.
10. Inoue E, Shimizu Y, Masui R, Usui M, Sudo K. Analgesic effects of Toad Cake and Toad-Cake-containing herbal drugs. J Pharmacopuncture 2014; 17: 074-9.
11. Mizuno K, Hisada S, Hishida H, Nomura M, Tsuchida T, Horiba M, et al. Effect of Kyushin on Congestive Heart Failure. Kiso to Rinsho 1978; 12: 961-80.
12. Mizuno K, Hisada S, Hishida H, Nomura M, Tsuchida T, Horiba M, et al. Effect of Kyushin on Congestive Heart Failure (Second Report). Kiso to Rinsho 1979; 13: 1692-720.
13. Weixiong L, Zhuoxiang J, Shilong L, Wangxiu W, Xia Y, Weiwei M. Clinical study of "Kyushin" on patients with qi deficiency and blood stasis in the treatment of coronary heart disease. J Tradit Chin Med 1998; 30: 34-6.
14. Qingming L, Jingfeng W, Guiming T. Clinical summary of 50 patients with qi deficiency and blood stasis in the treatment of coronary heart diseases of "Kyushin" (Author's translation). J Tradit Chin Med 1999; 9: 17-20.
15. Qingming L, Jingfeng W, Guiming T-Clinical summary of 50 patients with qi deficiency and blood stasis in the treatment of coronary heart diseases of "Kyushin" (Author's translation). J Tradit Chin Med 1999; 9: 17-20.
16. Cha K, Byung H, Won J. Bufotoxin poisoning that showed the sign of acute digitalis overdose in the patient of Kyushin® intoxication. Hong Kong J Emerg Med 2020; 27: 180-4.
17. Qi J, Zulfiker A, Li C, Good D, Wei M. The development of toad toxins as potential therapeutic agents. Toxins 2018; 10: 336-40.
18. Song T, Xi C, Xuan Z, Qiongtao S, Ying Z, Yuanyuan Z, et al. Bufalin, a butanolide steroid from the parotid glands of the Chinese toad, inhibits L-type Ca2+ channels and contractility in rat ventricular myocytes. Fundam Clin Pharmacol 2017; 31: 340-6.
19. Guo-lei W. Forty-Two Cases of Acute Non-ST Segment Elevation Myocardial Infarction Treated with Musk Kyushin Pills in Combination with Sofren Injection. Henan Tradit Chin Med 2017; 4: 20-4.
20. Li F, Weng Y, Wang L, He H, Yang J, Tang X. The efficacy and safety of bufadienolides-loaded nanostructured lipid carriers. Int J Pharm 2010; 393: 204-12.